CASE REPORT

Bagcilar Med Bull
DOI: 10.4274/BMB.galenos.2026.27146

PAX8 Can be Misleading in the Differential Diagnosis of Anaplastic Thyroid Carcinoma vs. High-grade Lymphoma on thyroid FNA: A Didactic Case Report

Tiroid İnce İğne Aspirasyon Biyopsisinde Anaplastik Tiroid Karsinomu ve Yüksek Dereceli Lenfoma Ayırıcı Tanısında PAX8 Yanıltıcı Olabilir: Didaktik Bir Olgu Sunumu

Eren Altun[1], İsmail Safa Poyrazoğlu[2], Cemal Özyılmaz[3]

[1]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Pathology, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Otolaryngology, İstanbul, Turkey
[3]Ordu University, Ordu Training and Research Hospital, Department of Otolaryngology, Ordu, Turkey

Abstract

A 74-year-old woman was investigated for a 56x30 mm concentric heterogeneous, isoechoic solid nodule in the left thyroid lobe. Fine needle aspiration was diagnosed as anaplastic carcinoma of the thyroid based on atypical cells that expressed PAX8 at the cell block material. However, biopsy confirmed a B-cell lymphoma. In this case report, we emphasize that the use of PAX8 immunohistochemistry may be misleading in thyroid lesions and that other possibilities should be kept in mind in the differential diagnosis.

Keywords: Anaplastic thyroid carcinoma, B-cell lymphoma, PAX8

Öz

Yetmiş dört yaşında bir kadın hastada, sol tiroid lobunda 56×30 mm boyutlarında, konsantrik, heterojen, izoekoik solid bir nodül saptanması üzerine ileri inceleme yapıldı. İnce iğne aspirasyon biyopsisinde, hücre bloğu materyalinde PAX8 ekspresyonu gösteren atipik hücrelerin varlığı nedeniyle anaplastik tiroid karsinomu tanısı konuldu. Ancak yapılan doku biyopsisinde B-hücreli lenfoma tanısı doğrulandı. Bu olgu sunumunda, tiroid lezyonlarında PAX8 immünohistokimyasının yanıltıcı olabileceği ve ayırıcı tanıda diğer olasılıkların da mutlaka göz önünde bulundurulması gerektiği vurgulanmaktadır.

Anahtar kelimeler: Anaplastik tiroid karsinomu, B-hücreli lenfoma, PAX8

Introduction

Anaplastic thyroid carcinoma (ATC) and thyroid lymphoma are rare thyroid malignancies (1). They pose significant challenges due to diagnostic difficulties and aggressive biology. Although most patients with ATC present with a rapidly growing neck mass, a small number are diagnosed based on pulmonary or skeletal metastases (2). The diagnosis of these lesions in the thyroid relies on biopsy

Address for Correspondence: Assoc. Prof. Eren Altun, University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Pathology, İstanbul, Turkey
E-mail: erenaltun@hotmail.com **ORCID:** orcid.org/0000-0001-9110-8364
Received: 08.02.2026 **Accepted:** 06.06.2026 **Epub:** 09.06.2026

Cite this article as: Altun E, Poyrazoğlu İS, Özyılmaz C. PAX8 can be misleading in the differential diagnosis of anaplastic thyroid carcinoma vs. high-grade lymphoma on thyroid FNA: a didactic case report. Bagcilar Med Bull. [Epub Ahead of Print]

Copyright© 2026 The Author(s). Published by Galenos Publishing House on behalf of Health Sciences University Turkey, İstanbul Bagcilar Training and Research Hospital. This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

and immunohistochemistry (IHC) is useful to identify the cellular origin, diagnosis, prognosis and genetic predisposition (3). Strong and widespread expression of PAX8 is seen in thyroid follicular epithelium and associated neoplasms, but this biomarker is also positive in renal cell carcinoma, gynecological tumors, and seminoma (3). In this case report, we emphasize that the use of PAX8 can be problematic in thyroid lesions and that other possibilities should be kept in mind in the differential diagnosis.

Case Report

A 74-year-old woman presented with a three-month history of a rapidly enlarging, painless swelling on the left side of the neck. Importantly, the patient had no known history of chronic lymphocytic (Hashimoto's) thyroiditis or any prior thyroid dysfunction. She has a 56x30 mm concentric heterogeneous, isoechoic solid nodule in the left thyroid lobe. Notably, the nodule exhibited internal heterogeneity and increased, irregular vascularization. Unlike typical lymphoma cases which often present as markedly hypoechoic with diffuse vascularity, the sonographic features in our patient were suspicious for an undifferentiated malignancy like ATC. Fine needle aspiration cytology of the thyroid gland and the largest lymph node showed malignant cytology (Bethesda VI) with increased cellularity, epithelioid/epithelial-cell pattern with nuclear enlargement and irregular nuclear membranes in all cells, apoptosis and necrosis (Figure 1a, 1b). Immunohistochemical studies of the cell block material showed weak but diffuse positivity for PAX8 (Mouse monoclonal PAX-8 Antibody, Clone BC12, GenomeMe Antibody, 1/120, Richmond, Canada) (Figure 1c). An external positive control (kidney tissue) was used and showed appropriate staining. Thyroglobulin was focally positive; and the Ki-67 labeling index was 50-60%. A contrast-enhanced MR image of the neck revealed a sizable cervical mass originating from the thyroid gland, extending into the right cervical soft tissue. The mass caused displacement of the trachea, with lymph nodes on both sides appearing as conglomerated.

The case was discussed in the tumor board, and the distinction between ATC and other malignancies could not be confirmed, therefore excisional biopsy was performed from the superficial lymph node at level 5 on the right side. Pathological examination of the lymph node revealed atypical neoplastic cell infiltration with large vesicular nuclei, prominent nucleoli, and large eosinophilic cytoplasm which completely erased the lymph node structure (Figure 2a). Immunohistochemical studies

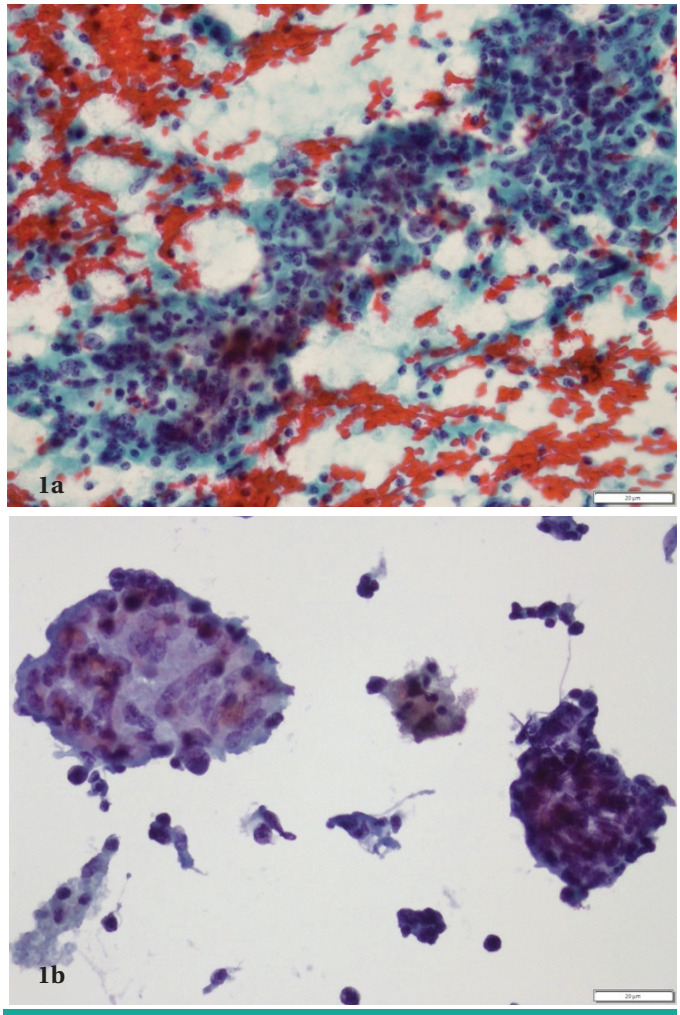

Figure 1a, **1b.** In the FNA slides shows a mixture of large, irregularly shaped cells with marked pleomorphism. The nuclei are hyperchromatic, irregular, and often enlarged. (PAP and Giemsa, 400x)

FNA: Fine needle aspiration

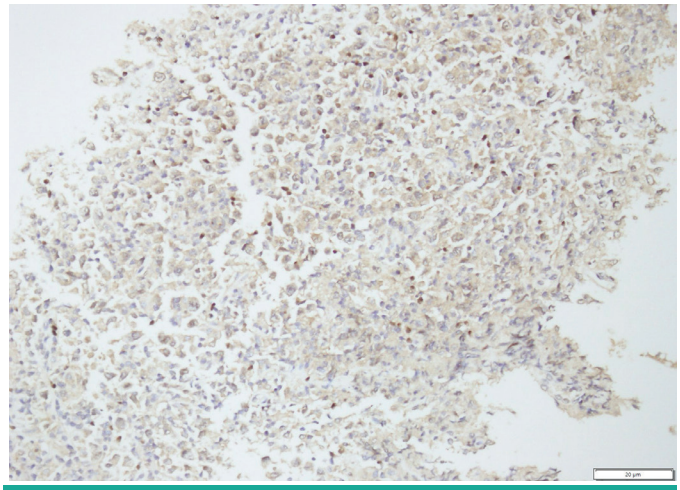

Figure 1c. Immunohistochemical studies of the material showed weak but diffuse positivity for PAX8 (anti-PAX, 100x)

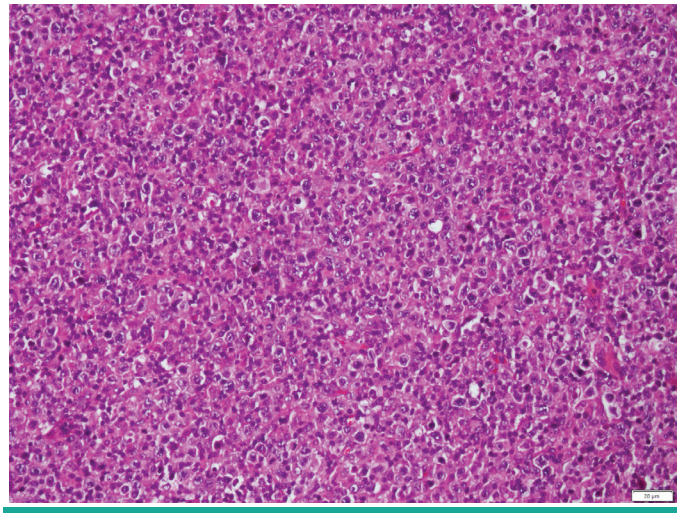

Figure 2a. In the H&E slides, the lymph node revealed atypical neoplastic cell infiltration with large vesicular nuclei, prominent nucleoli, and large eosinophilic cytoplasm, which completely erased the lymph node structure (H&E, 200x)

H&E: Hematoxylin&eosin

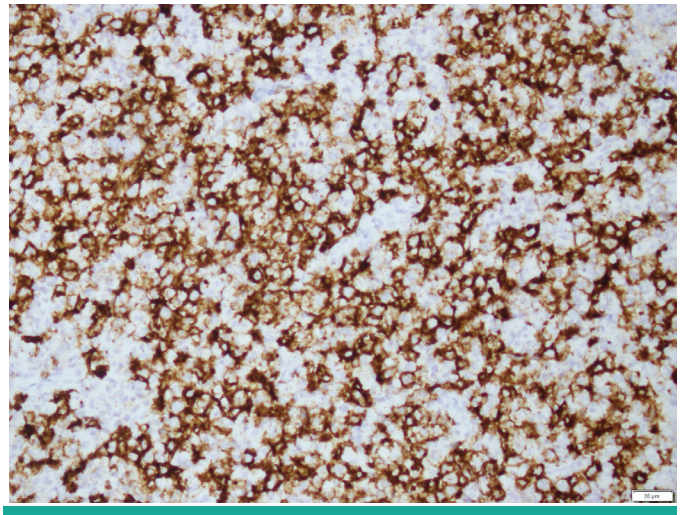

Figure 2b. Immunohistochemical studies of infiltrative neoplastic cells showed diffuse positivity for CD20 (anti-CD20, 100x)

of the material showed positivity in the tumor cells for CD20 and CD79a, focal positivity for CD30, and 85-90% reactivity for K-i67 (Figure 2b). Based on the morphological and immunohistochemical findings, a diagnosis of non-germinal center high-grade diffuse large B-cell lymphoma with CD30-positive anaplastic features was established, and the patient was referred to the hematology department for further management.

Written informed consent was obtained from the patient for the publication of this case report. All procedures were conducted in accordance with ethical standards, and patient identity was kept confidential.

Discussion

PAX8 is a paired-box family transcription factor that plays a critical role in thyroid gland development and the maintenance of its functional integrity (4). PAX8 expression is observed in renal tubular epithelium, fallopian tube epithelium, ovarian inclusion cysts, and lymphoid follicles, and it is also detected in tumors such as renal cell carcinoma, nephroblastoma, seminoma, and ovarian carcinoma. Owing to this expression profile, PAX8 serves as a valuable immunohistochemical marker in the diagnosis of anaplastic carcinomas, particularly when pulmonary carcinoma is considered in the differential diagnosis (5). PAX8 expression has been shown to be frequently preserved in cases of ATC and to be helpful in cases with limited or absent expression of TTF1 and cytokeratins, particularly those lacking the well-differentiated thyroid carcinoma component (6).

Multiple commercially available antibodies targeting PAX8 have been described in the literature. Among these, one of the most frequently utilized is a polyclonal antiserum directed against the N-terminal DNA-binding domain of PAX8, corresponding to amino acids 1-212 (7). Thyroid follicular cells are positive using both N-terminal and C-terminal PAX8 antibodies; on the other hand, N-terminal PAX8 antibodies react with B-cells, while C-terminal PAX8 antibodies are negative for B-cells (7). PAX8 expression has been reported in B-lymphocytes in both normal lymphoid organs and hematological neoplasms, and lymphocytes were used as internal positive control for PAX8 immunostaining (8). It is critical to know the specificity of the antiserum/antibody being used and to be aware of its range of reactivites (9).

Primary thyroid lymphoma represents approximately 5% of all malignant thyroid tumors. Secondary lymphomatous involvement of the thyroid is associated with a poorer prognosis and higher mortality compared with primary disease. Among histological subtypes, diffuse large B-cell lymphoma is the most frequently encountered, comprising over half of reported cases, followed by mucosa-associated lymphoid tissue lymphoma and less common entities including follicular lymphoma, small lymphocytic lymphoma, Hodgkin lymphoma, Burkitt lymphoma, as well as T-cell and mantle cell lymphomas (10). ATC can be easily confused with nonthyroidal malignancies such as lymphoma, sarcoma, and head and neck squamous

cell carcinoma (6,11). Both thyroid lymphoma and ATC typically present in elderly patients as rapidly enlarging neck masses and may lead to symptoms related to tracheal or laryngeal compression. ATC carries an extremely poor prognosis, with mortality exceeding 95%, and only rare cases achieve cure with combined modalities such as surgery, radiotherapy, and multi-agent chemotherapy. In contrast, thyroid lymphoma generally demonstrates an excellent response to chemotherapy and is associated with a favorable prognosis (12). In this case, the initial panel was limited to PAX8 and thyroglobulin due to the strong clinical suspicion of ATC. The omission of a pan-leukocyte marker (CD45) or B-cell markers in the first-line IHC panel on the cell block material represents a diagnostic limitation that contributed to the initial misdiagnosis. When an undifferentiated thyroid tumor is suspected, lymphoma must be definitively ruled out before initiating aggressive surgical or radiation therapy, as the primary treatment for lymphoma is chemotherapy and carries a significantly better prognosis. To ensure diagnostic accuracy, a systematic approach should be followed: Initially, the clinical history (e.g., prior Hashimoto's thyroiditis or pain level) and ultrasonographic patterns (e.g., irregular vascularity vs. hypoechoicity) must be assessed. If PAX8 positivity is detected, the specific antibody clone must be verified, and a mandatory lymphoid panel including CD20 and CD79a should be performed to differentiate between B-cell lymphoma and ATC. In the present case, lymphoma was initially omitted from the differential diagnosis during the FNA stage. This was primarily due to the predominance of pleomorphic epithelioid cell morphology and the presence of extensive necrosis, which are more characteristic of ATC than typical lymphoid malignancies. Furthermore, the absence of a known history of chronic lymphocytic (Hashimoto's) thyroiditis led the clinical team to prioritize undifferentiated epithelial malignancies. This case underscores that in the setting of high-grade thyroid malignancies, clinicians and pathologists should maintain a high index of suspicion for lymphoma, even when cytomorphology appears deceptively epithelial.

In this case report, it is emphasized that the use of PAX8 IHC can be misleading in thyroid lesions and that possibilities other than thyroid follicular neoplasms should be kept in mind in the differential diagnosis. The clinical impact of misdiagnosing lymphoma as ATC is profound. Patients may be subjected to unnecessary, aggressive surgical interventions with significant morbidity, whereas primary thyroid lymphoma typically requires non-surgical, chemotherapy-based management with a much better prognosis. It is critically important that pathologists are fully aware of the reactivities of the antibodies and clones used in the assessment of cases, as this can impact the differential diagnosis.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report. All procedures were conducted in accordance with ethical standards, and patient identity was kept confidential.

Acknowledgments

We sincerely thank Prof. Dr. Sylvia Asa for their insightful feedback, which significantly contributed to the quality of this study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.S.P., Concept: E.A., Design: E.A., İ.S.P., C.Ö., Data Collection or Processing: E.A., İ.S.P., C.Ö., Analysis or Interpretation: E.A., İ.S.P., Literature Search: C.Ö., Writing: E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Untch BR, Olson JA Jr. Anaplastic thyroid carcinoma, thyroid lymphoma, and metastasis to thyroid. Surg Oncol Clin N Am. 2006;15(3):661-79, x.
2. McIver B, Hay ID, Giuffrida DF, Dvorak CE, Grant CS, Thompson GB, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. Surgery. 2001;130(6):1028-1034.
3. Baloch Z, Mete O, Asa SL. Immunohistochemical biomarkers in thyroid pathology. Endocr Pathol. 2018;29(2):91-112.
4. Pasca di Magliano M, Di Lauro R, Zannini M. Pax8 has a key role in thyroid cell differentiation. Proc Natl Acad Sci U S A. 2000;97(24):13144-13149.
5. Nonaka D, Tang Y, Chiriboga L, Rivera M, Ghossein R. Diagnostic utility of thyroid transcription factors Pax8 and TTF-2 (FoxE1) in thyroid epithelial neoplasms. Mod Pathol. 2008;21(2):192-200.
6. Bishop JA, Sharma R, Westra WH. PAX8 immunostaining of anaplastic thyroid carcinoma: a reliable means of discerning thyroid origin for undifferentiated tumors of the head and neck. Hum Pathol. 2011;42(12):1873-1877.
7. Moretti L, Medeiros LJ, Kunkalla K, Williams MD, Singh RR, Vega F. N-terminal PAX8 polyclonal antibody shows cross-reactivity with N-terminal region of PAX5 and is responsible for reports of PAX8 positivity in malignant lymphomas. Mod Pathol. 2012;25(2):231-236.

8. Laury AR, Perets R, Piao H, Krane JF, Barletta JA, French C, et al. A comprehensive analysis of PAX8 expression in human epithelial tumors. Am J Surg Pathol. 2011;35(6):816-826.

9. Gucer H, Caliskan S, Kefeli M, Mete O. Do you know the details of your PAX8 antibody? Monoclonal PAX8 (MRQ-50) is not expressed in a series of 45 medullary thyroid carcinomas. Endocr Pathol. 2020;31(1):33-38.

10. Rezkallah E, Hanna RS, Elsaify WM. Thyroid lymphoma: case series review. Am Surg. 2023;89(11):4811-4816.

11. Mneimneh WS, Asa SL. Divergent lineage markers in anaplastic thyroid carcinoma. Am J Surg Pathol. 2024;48(2):230-237.

12. Daneshbod Y, Omidvari S, Daneshbod K, Negahban S, Dehghani M. Diffuse large B cell lymphoma of thyroid as a masquerader of anaplastic carcinoma of thyroid, diagnosed by FNA: a case report. Cytojournal. 2006;3:23.